CLAIMS

What is claimed is:

1. A metallo-construct comprising a metal ion-binding backbone for complexing with a metal ion, and a biological-function domain, which biological-function domain is conformationally constrained upon complexing the metal ion-binding backbone with a metal ion.

2. The construct of claim 1, wherein at least a portion of the construct is conformationally constrained in a secondary structure upon complexing the metal ion-binding backbone with the metal ion.

3. The construct of claim 2, wherein the construct has a conformationally constrained global structure upon complexing the metal ion-binding backbone with the metal ion.

4. A manufactured peptide and pharmaceutically acceptable salts thereof comprising a metal ion-binding backbone including two or more contiguous amino acids available for complexing with a metal ion, and a biological-function domain, which biological-function domain is conformationally constrained upon complexing the metal ion-binding backbone with a metal ion.

5. The peptide of claim 4, wherein at least a portion of the peptide is conformationally constrained in a secondary structure upon complexing the metal ion-binding backbone with the metal ion.

6. The peptide of claim 5, wherein the peptide has a conformationally constrained global structure upon complexing the metal ion-binding backbone with the metal ion.

7. The peptide of claim 4, wherein the biological-function domain is substantially more potent upon the metal ion-binding backbone being complexed with the metal ion.

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8. The peptide of claim 4, wherein all of the valences of the metal ion are satisfied upon complexation of the metal ion.

9. The peptide of claim 4, wherein the metal ion-binding backbone comprises a plurality of amino acids each containing at least one nitrogen, sulfur or oxygen atom available for complexing with the available valences of the metal ion.

10. The peptide of claim 9 wherein if less than all of the valences of the metal ion would otherwise be satisfied upon complexation of the metal ion with the amino acids comprising the metal ion-binding backbone, then the metal ion-binding backbone also comprises a derivatized amino acid or spacer sequence, which derivatized amino acid or spacer sequence comprises at least one nitrogen, sulfur or oxygen atom available for complexing with the available valences of the metal ion, so that all of said valences of the metal ion are satisfied upon complexation of the metal ion.

11. The peptide of claim 4, wherein the biological-function domain comprises a ligand capable of forming a member of a ligand and receptor pair.

12. The peptide of claim 11, wherein the affinity of the ligand for its receptor is substantially higher when the metal ion-binding backbone is complexed with the metal ion than is the affinity of the ligand for its receptor when the metal ion-binding backbone is not complexed with the metal ion.

13. The peptide of claim 4, wherein the metal ion-binding backbone is complexed with a metal ion.

14. The peptide of claim 4 wherein the peptide is a cyclic peptide.

15. The peptide of claim 4 wherein upon complexing the metal ion-binding backbone with the metal ion the biological-function domain is sychnological.

16. The peptide of claim 4 wherein upon complexing the metal ion-binding backbone with the metal ion the biological-function domain is rhegnylogical.

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17. A manufactured peptide and pharmaceutically acceptable salts thereof with a conformationally constrained secondary structure upon complexing with a metal ion, the conformationally constrained secondary structure comprising a member of a ligand and receptor pair, said peptide being of the general formula:

$$R_1\text{-}X\text{-}R_2$$

wherein X is a complexing backbone for complexing a metal ion comprising a plurality of contiguous amino acids, so that substantially all of the valences of the metal ion are satisfied upon complexation of the metal ion with X;

wherein X has, upon complexing with the metal ion, a specific regional secondary structure forming at least a part of the global secondary structure;

wherein R_1 and R_2 each comprise from 0 to about 20 amino acids, said amino acids being selected so that upon complexing the metal ion with X at least a portion of either R_1 or R_2 or both have a structure forming the balance of the conformationally constrained secondary structure; and

wherein the conformationally constrained secondary structure comprising at least a part of X, R_1 or R_2 comprises a ligand capable of forming a member of a ligand and receptor pair.

18. The peptide of claim 17 wherein if less than all of the valences of the metal ion are otherwise satisfied upon complexation of the metal ion with the amino acids comprising X, then X also comprises a derivatized amino acid or spacer sequence, which derivatized amino acid or spacer sequence comprises at least one nitrogen, sulfur or oxygen atom available for complexing with the available valences of the metal ion, so that all of said valences of the metal ion are satisfied upon complexation of the metal ion with X.

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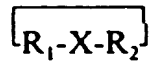
19. The peptide of claim 17 which is a cyclic peptide of the formula:

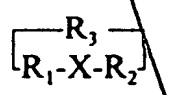


wherein R_1 and R_2 are covalently linked together.

20. The cyclic peptide of claim 19 wherein R_1 and R_2 are covalently linked together through an amide, disulfide, thioether, thioester, urethane, or ester linkages.

21. The cyclic peptide of claim 19 wherein the covalent linkage between R_1 and R_2 is a linkage through the end groups of R_1 and R_2, linkage through side chain functionalities of any amino acid within R_1 and R_2, linkage through the end group of R_1 and a side chain functionality of any amino acid in R_2, or linkage through the end group of R_2 and a side chain functionality of any amino acid in R_1.

22. The cyclic peptide of claim 19 which is a cyclic peptide of the formula:



wherein R_3 comprises from 1 to about 20 amino acids.

23. The cyclic peptide of claim 22 wherein R_3 forms a part of the conformationally constrained secondary structure.

24. The peptide of claim 17 wherein X, upon complexing with a metal ion, forms a specific regional secondary structure which is a reverse turn structure.

25. A manufactured peptide and pharmaceutically acceptable salts thereof comprising a metal ion-binding backbone including two or more contiguous amino acids available for complexing with a metal ion, and a biological-function domain specific for receptors to the tripeptide sequence Arg-Gly-Asp, which biological-function domain is conformationally constrained upon complexing the metal ion-binding backbone with a metal ion.

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26. The peptide of claim 25 of the formulas:

R_1-Aaa-Bbb-Ccc-Ddd-R_2,

R_1-Bbb-Aaa-Ccc-Ddd-R_2,

R_1-Bbb-Ddd-Ccc-Aaa-R_2, or

R_1-Ddd-Bbb-Ccc-Aaa-R_2

wherein

Aaa is an L- or D-isomer of an amino acid with a positively charged side chain, and containing a nitrogen which can be available for binding a metal ion;

Bbb is an L- or D-isomer of an amino acid with one or more uncharged side chains;

Ccc is an L- or D-isomer of an amino acid containing a sulfur and a nitrogen or containing two nitrogens which can be available for binding a metal ion;

Ddd is an L- or D-isomer of a neutral amino acid with a free α-carboxyl group or an amino acid with a negatively charged functional group in its side chain;

R_1 is H, alkyl, aryl, alkylcarbonyl, arylcarbonyl, alkyloxycarbonyl, aryloxycarbonyl, or a polymer attached directly or through a carbonyl group; and

R_2 is, if Ddd is other than a neutral amino acid with a free α-carboxyl group, an amide, substituted amide or ester.

27. A manufactured peptide and pharmaceutically acceptable salts thereof comprising a metal ion-binding backbone including two or more contiguous amino acids available for complexing with a metal ion, and a biological-function domain specific for the tuftsin receptor, which biological-function domain is conformationally constrained upon complexing the metal ion-binding backbone with a metal ion.

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28. The peptide of claim 27 of the formula:

R_1-Aaa-Bbb-Ccc-Ddd-Eee-R_2

wherein

Aaa is a L- or D-isomer of an amino acid with a neutral or hydrophilic side chain;

Bbb is an L- or D-isomer of an amino acid with a positively charged side chain containing a nitrogen which can be available for binding a metal ion;

Ccc is an L- or D-isomer of an amino acid with an uncharged side chain and containing a nitrogen which can be available for binding a metal ion;

Ddd is an L- or D-isomer of an amino acid containing a sulfur, a sulfur and a nitrogen, or two nitrogens which can be available for binding a metal ion;

Eee is an L- or D-isomer of an amino acid with a positively charged side chain;

R_1 is H, alkyl, aryl, alkylcarbonyl, arylcarbonyl, alkyloxycarbonyl, aryloxycarbonyl, or a polymer attached directly or through a carbonyl group, unless Aaa is a des-amino amino acid, in which case R_1 does not exist; and

R_2 is an amide, substituted amide, ester, or a polymer unless Eee is a des-carboxyl amino acid, in which case R_2 does not exist.

29. A cyclic peptide, and pharmaceutically acceptable salts thereof, with a metal ion-binding backbone for isosteric replacement of a disulfide, thioether, lactam, or a lactone bridge, said cyclic peptide being of the general formula:

$$R_1\text{-Aaa-}R_3\text{-Bbb-}R_2$$
(X bridges Aaa and Bbb)

wherein X is a complexing backbone for complexing metal ion comprising a plurality of amino acids, so that substantially all of said valences of the metal ion are satisfied upon complexation of the metal ion with X,

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wherein R_1 and R_2 each comprise from 0 to about 20 amino acids,

wherein R_3 comprises from 1 to about 20 amino acids,

wherein Aaa and Bbb each comprise an amino acid connected to X through a disulfide, amide, thioether, thioester, urethane or ester bond.

30. The cyclic peptide of claim 29, wherein X is an amino acid sequence of the formula:

Ccc-Ddd-Eee or Eee-Ddd-Ccc,

wherein each of Ccc and Ddd is an amino acid or dipeptide with uncharged side chains, and

wherein Eee is a L- or D-isomer of Cys, HomoCys, Pen, or His.

31. A method of making a peptide and pharmaceutically acceptable salts thereof that has a conformationally constrained secondary structure obtained upon complexing with a metal ion, the method comprising the steps of:

a) providing a peptide of the general formula:

R_1-X-R_2

wherein X is a complexing backbone for complexing metal ion comprising a plurality of contiguous amino acids, so that substantially all of said valences of the metal ion are satisfied upon complexation of the metal ion with X,

wherein X has, upon complexing with the metal ion, a specific regional secondary structure forming a part of the secondary structure, and

wherein R_1 and R_2 each comprise from 0 to about 20 amino acids, said amino acids being selected so that upon complexing the metal ion with X at least a portion of either R_1 or R_2 or both have a structure forming the balance of the conformationally constrained secondary structure; and

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b) complexing a metal ion to the peptide.

32. A method of making a peptide or pharmaceutically acceptable salts thereof that comprises a conformationally constrained secondary structure comprising a ligand capable of forming a member of a ligand and receptor pair, the method comprising the steps of:

a) providing a peptide of the general formula:

R_1-X-R_2

wherein X is a complexing backbone for complexing metal ion comprising a plurality of amino acids, so that substantially all of said valences of the metal ion are satisfied upon complexation of the metal ion with X,

wherein X has, upon complexing with the metal ion, a specific regional secondary structure forming a part of the conformationally constrained secondary structure,

wherein R_1 and R_2 each comprise from 0 to about 20 amino acids, said amino acids being selected so that upon complexing the metal ion with X at least a portion of either R_1 or R_2 or both have a structure forming the balance of the conformationally constrained global secondary structure, and

wherein the conformationally constrained global secondary structure comprising at least a part of X, R_1 or R_2 comprises a ligand capable of forming a member of a ligand and receptor pair; and

b) complexing a metal ion to the peptide;

whereby the metal ion causes X to form a specific regional secondary structure, thereby causing the peptide to be configured as a conformationally constrained secondary structure comprising a ligand capable of forming a member of a ligand and receptor pair.

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33. A method of making a peptide or a pharmaceutically acceptable salt thereof that includes an amino acid sequence which mimics a biological-function domain, the method comprising the steps of:

a) providing a complexing backbone for complexing a metal ion comprising a plurality of amino acids, said amino acids being selected so that substantially all of the valences of the metal ion are satisfied upon complexation of the metal ion with the complexing backbone, which complexing backbone is coextensive with at least a portion of the biological-function domain upon complexing of the complexing backbone with a metal ion;

b) providing from 0 to about 20 amino acids linked to either end of the complexing backbone, which amino acids comprise the remainder of the biological-function domain upon complexing of the complexing backbone with a metal ion; and

c) complexing the complexing backbone with a metal ion.

34. A peptide-based pharmaceutical composition comprising

a peptide comprising a metal ion-binding backbone and a determined biological-function domain, which biological-function domain is conformationally constrained upon complexing the metal ion-binding backbone with a metal ion; and

a metal ion.

35. A method of obtaining a metallopeptide having a desired target property, comprising the steps of:

a) providing a mixture of candidate peptides, each peptide comprising a metal ion-binding backbone with two or more contiguous amino acids available for complexing with a metal ion, and which metal ion-binding backbone is conformationally constrained upon complexing the metal ion-binding backbone with a metal ion, each peptide further comprising distinct, unique and different amino acid sequences, wherein the presence of each peptide in the mixture is predetermined;

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b) complexing the metal ion-binding backbone of the peptides with a metal ion; and

c) selecting from among the mixture of candidate metallopeptides a metallopeptide having a desired target property by exposing the mixture of candidate metallopeptides to a substance to which a metallopeptide with the desired target property will preferentially bind.

36. The method as claimed in claim 35, further comprising isolating the selected candidate metallopeptide having the desired target property.

37. A method of obtaining a metallopeptide having a desired target property, comprising the steps of:

a) providing known combinations of two, three or four contiguous amino acids comprising a metal ion-binding backbone wherein each amino acid is available for complexing with a metal ion, and further wherein the metal ion-binding backbone is conformationally constrained upon complexing the metal ion-binding backbone with a metal ion;

b) adding distinct, unique and different amino acid sequences, each sequence comprising one or more amino acids, to the amino acids comprising a metal ion-binding backbone, wherein the presence of each peptide in the mixture is predetermined;

c) complexing the metal ion-binding backbone of the peptides with a metal ion; and

d) selecting from among the mixture of candidate metallopeptides a metallopeptide having a desired target property by exposing the mixture of candidate metallopeptides to a substance to which a metallopeptide with the desired target property will preferentially bind.

38. The method as claimed in claim 37, further comprising isolating the selected candidate metallopeptide having the desired target property.

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39. A method of obtaining a metallopeptide having a desired biological-function domain, comprising the steps of:

a) providing known combinations of two, three or four contiguous amino acids comprising a metal ion-binding backbone wherein each amino acid is available for complexing with a metal ion, and further wherein the metal ion-binding backbone is conformationally constrained upon complexing the metal ion-binding backbone with a metal ion;

b) adding distinct, unique and different amino acid sequences, each sequence comprising one or more amino acids, to the contiguous amino acids comprising a metal ion-binding backbone, wherein the presence of each peptide in the mixture is predetermined;

c) complexing the metal ion-binding backbone of the peptides with a metal ion; and

d) selecting from among the mixture of candidate metallopeptides a metallopeptide having a desired biological-function domain by exposing the mixture of candidate metallopeptides to a substance to which a peptide with the desired biological-function domain will preferentially bind.

40. The method as claimed in claim 39, further comprising isolating the selected candidate metallopeptide having the desired biological-function domain.

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